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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/707,747
Filing Date: January 08, 2004
Appellant(s): PAUL ET AL.

Thomas E. Toner
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed June 25, 2007 appealing from the Office action mailed January 23, 2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after non-final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Yoon et al. "A single origin of the peridinin- and fucoxanthin-containing plastids in dinoflagellates through tertiary endosymbiosis" Proc. Natl. Acad. Sci. USA Vol. 99, No. 18 (2002), pp. 11724-11729.

Buck et al. "Design strategies and performance of custom DNA sequencing primers" BioTechniques Vol. 27, No. 3 (1999), pp. 528-536.

Yoon et al. "*Karenia brevis* ribolose-1,5-bisphosphate carboxylase/oxygenase (rbcL) gene, partial cds" GenBank Accession No. AY119786 (2002).

Bowers et al. "Development of real-time PCR assays for rapid detection of *Pfiesteria piscicida* and related dinoflagellates" Applied Environmental Microbiol. Vol. 66, No. 11 (2000), pp. 4641-4648.

Wilson et al. "Species-specific detection of hydrocarbon-utilizing bacteria" J. Microbiol. Meth. Vol. 39 (1999), pp. 59-78.

Leone et al. "Molecular beacon probes combined with amplification by NASBA enable homogeneous, real-time detection of RNA" Nucleic Acids Res. Vol. 26, No. 9 (1998), pp. 2150-2155.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 16-18 are rejected under 35 U.S.C. 103(a) as being anticipated by Yoon et al. (Proc. Natl. Acad. Sci. USA. (2002) 99: 11724-11729) in view of Buck et al. (Biotechniques (1999) 27: 528-536) and further in view of GenBank Accession No. AY119786.

With regard to claim 16, Yoon teaches a method for screening a sample for the presence of *K. brevis,* comprising:

subjecting the sample to amplification using a pair of oligonucleotide primers capable of amplifying a target region of the ribulose 1,5-biphosphate carboxylase-oxygenase large subunit (rbcL) of *K. brevis* (amplification using species-specific primers, p. 11725, column 1, lines 13-24 and Table 2, supporting information); and

assaying the mRNA for the presence of the amplified target region of the ribulose 1,5-biphosphate carboxylase-oxygenase large subunit (rbcL) unique *K. brevis* (PCR products generated from total RNA were sequenced using dye terminators as probes, p. 11725, column 1, lines 20-29; sequences are unique to *K. brevis,* p. 11726, column 1, lines 8-14 and Figure 1A and B and GenBank Accession No. AY119786; BLAST search indicates primers amplify a region unique to *K. brevis*, see BLAST results).

With regard to claim 17, Yoon teaches a method wherein the pair of oligonucleotide primers specifically amplify mRNA of a target region of the ribulose 1,5-biphosphate carboxylase-oxygenase large subunit (rbcL) of *K. brevis* and do not amplify a region of the ribulose 1,5-biphosphate carboxylase-oxygenase large subunit (rbcL) of *K. mikimotoi* (detection of *K. brevis* is performed by amplification using species-specific primers, p. 11725, column 1, lines 13-24 and Table 2, supporting information; BLAST search indicates primers amplify a region unique to *K. brevis* and not other *Karenia* species such as *K. mikimotoi*, see BLAST results).

With regard to claim 18, Yoon teaches a method wherein the target region of the ribulose 1,5-biphosphate carboxylase-oxygenase large subunit (rbcL) of *K. brevis* is about 87 to 91 base pairs in length (using primers rbcL64F and R-173 in Table 1, a 155-base pair target would be amplified in rbcL gene region, p. 11724, column 2, lines 29-32, Table 1, supporting information and GenBank Accession No. AY119786).

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Yoon, which are 100% derived from sequences expressly suggested by the prior art of Yoon as useful for primers for the detection *K. brevis,* and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked

(see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Claims 19-21, 24, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoon et al. (Proc. Natl. Acad. Sci. USA. (2002) 99: 11724-11729) in view of Bowers et al. (Appl. Environ. Microbiol. (2000) 66: 4641-4648) and further in view of Wilson et al. (J. Microbiol. Meth. (1999) 39:59-78) and further in view of Buck et al. (Biotechniques (1999) 27: 528-536) and further in view of GenBank Accession No. AY119786.

Yoon, in view of Buck and GenBank Accession No. AY119786, teaches the limitations of claims 16-18 as discussed above.

With regard to claims 20 and 21, Yoon also teaches a method wherein the pair of oligonucleotide primers consist of SEQ. ID. No. 1 (Table 1, supporting information, GeneBank Accession No. AY119786, positions 729-748) and SEQ. ID. No. 2 (Table 1,

supporting information, GeneBank Accession No. AY119786, positions 819-798), wherein SEQ. ID. No. 1 comprises a forward primer (GeneBank Accession No. AY119786, positions 729-748) and SEQ. ID. No. 2 comprises a reverse primer (GeneBank Accession No. AY119786, positions 819-798), to generate a 91-base pair amplicon (from positions 729 to 819 of GeneBank Accession No. AY119786).

With regard to claims 24 and 25, Yoon also teaches a method wherein the amplification process is applied to the sample in the presence of a probe, wherein the probe consists of SEQ. ID. No. 6 (Table 1, supporting information, GeneBank Accession No. AY119786, positions 703-726).

Yoon does not teach a method for screening a sample for the presence of *K. brevis* using a real-time reverse transcriptase polymerase chain reaction or quantitative thermocycling. Yoon also does not teach methods of designing species-specific primer sets to amplify unique regions of the rbcL gene of *K. brevis* including primers consisting of SEQ ID Nos. 1 and 2 and a probe consisting of SEQ ID No. 6.

Bowers teaches a method of specifically detecting harmful algal bloom species including dinoflagellates such as *Pfiesteria* using a real-time polymerase chain reaction (p. 4643, column 1, lines 19-23) and internal probes (p. 4643, column 1, lines 23-30 and p. 4645, column 1, lines 8-14). Bowers demonstrates specific detection of *Pfiesteria* species in the presence of negative control samples including other harmful dinoflagellate species such as *K. brevis* (p. 4645, column 1, line 37 to column 2, line 13 and Table 1, *Gymnodinium breve=K. brevis*).

Bowers does not teach the detection of *K. brevis* sequences by the real time polymerase chain reaction using at least one specific primer and a probe. Bowers also does not teach methods of designing species-specific primer sets to amplify unique regions of the rbcL gene of *K. brevis,* including primers consisting of SEQ ID Nos. 1 and 2 and a probe consisting of SEQ ID No. 6.

Wilson teaches methods of designing species-specific primer sets by sequence alignment techniques in order to amplify unique regions of the 16S rRNA gene for purposes of detecting different microorganisms in water samples (p. 60, column 2, lines 5-16, p. 62, column 1, lines 35-40 and Figure 1).

Wilson does not teach a method for screening a sample for the presence of *K. brevis* using a real-time reverse transcriptase polymerase chain reaction or quantitative thermocycling. Wilson also does not teach methods of designing species-specific primer and probe sets to amplify unique regions of the rbcL gene of *K. brevis,* including primers consisting of SEQ ID Nos. 1 and 2 and a probe consisting of SEQ ID No. 6.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Yoon, Bowers and Wilson since Yoon teaches the detection of a sequence specific to *K. brevis* in the rbcL gene using a reverse-transcriptase polymerase chain reaction method, while Bowers describes a real-time polymerase chain reaction using an internal fluorescent probe to detect harmful dinoflagellates in a rapid, homogeneous assay, and Wilson teaches methods to design species-specific primers in order to detect single species in samples containing many different related or unrelated species. Thus, an ordinary practitioner

would have been motivated to combine these methods to provide a rapid test for harmful algal bloom species that results in an added level of specificity compared with assays based on traditional PCR methodology. The use of a high through-put real-time PCR assay greatly improves upon other traditional methods of processing large numbers of environmental water samples such as scanning electron microscopy which are very labor-intensive, and also provides a method that is more easily adapted for field-based testing. Furthermore, the methods of Wilson provide a highly powerful approach to species-specific detection using competitive PCR since unique primer sets that can be designed for multiplexed assays (Wilson, p. 74, column 2, lines 3-8, and also those containing internal controls by using universal primers sets in conserved regions of the target gene (Wilson, p. 72, column 2, line 43 to p. 73, column 1, line 8).

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Yoon, which are 100% derived from sequences expressly suggested by the prior art of Yoon as useful for primers for the detection *K. brevis,* and

concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical

sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Claims 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoon et al. (Proc. Natl. Acad. Sci. USA. (2002) 99: 11724-11729) in view of Leone et al. (Nucleic Acids Res. (1998) 26: 2150-2155) and further in view of Wilson et al. (J. Microbiol. Meth. (1999) 39:59-78) and further in view of Buck et al (Biotechniques (1999) 27: 528-536) and further in view of GenBank Accession No. AY119786.

Yoon, in view of Buck and GenBank Accession No. AY119786, teaches the limitations of claims 16-18 as discussed above.

With regard to claims 27 and 30, Yoon also teaches a method wherein the pair of oligonucleotide primers specific to a target region of the ribulose 1,5-biphosphate carboxylase-oxygenase large subunit (rbcL) of *K. brevis* consist of SEQ. ID. NO. 4 (Table 1, supporting information, Gene Bank Accession No. AY119786, positions 733-751) and SEQ. ID. No. 5 (Table 1, supporting information, Gene Bank Accession No. AY119786, positions 819-798, representing the 22 3-prime most bases of this NASBA primer complementary to the target; the remaining portion SEQ ID No. 5 serves as a

transcription initiation sequence, see Leone, Figure 6), to generate an 87-base pair amplicon (from positions 733 to 819 of GeneBank Accession No. AY119786).

With regard to claim 29, Yoon also teaches a method wherein the probe comprises a nucleotide sequence consisting of SEQ. ID. No. 3 (Table 1, supporting information, Gene Bank Accession No. AY119786, positions 758-775).

Yoon does not teach a method of screening a sample for the presence of *K. brevis* using nucleic acid sequence based amplification in the presence of a probe, including primers consisting of SEQ ID Nos. 4 and 5 and a probe consisting of SEQ ID No. 3.

With regard to claims 26-30, Leone teaches a method of homogeneous real-time detection of RNA using nucleic acid sequence based amplification and molecular beacon probes (p. 2151, column 1, lines 6-15 and line 42 to column 2, line 12).

Leone does not teach a method of detection of *K. brevis* sequences by nucleic acid sequence based amplification using at least one specific primer and a probe including primers consisting of SEQ ID Nos. 4 and 5 and a probe consisting of SEQ ID No. 3.

Wilson teaches methods of designing species-specific primer sets by sequence alignment techniques in order to amplify unique regions of the 16S rRNA gene for purposes of detecting different microorganisms in water samples (p. 60, column 2, lines 5-16, p. 62, column 1, lines 35-40 and Figure 1).

Wilson does not teach a method for screening a sample for the presence of *K. brevis* using a real-time reverse transcriptase polymerase chain reaction or quantitative

thermocycling. Wilson also does not teach methods of designing species-specific primer and probe sets to amplify unique regions of the rbcL gene of *K. brevis,* including primers consisting of SEQ ID Nos. 4 and 5 and a probe consisting of SEQ ID No. 3.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Yoon, Leone and Wilson since Yoon teaches the detection of a sequence specific to *K. brevis* in the rbcL gene using a reverse-transcriptase polymerase chain reaction method, while Leone teaches an alternative method of DNA detection, nucleic acid sequence-based amplification (NASBA), that can also be adapted to a real-time format, and thus is very suitable for detection of dinoflagellate species such as *K. brevis,* and Wilson teaches methods to design species-specific primers in order to detect single species in samples containing many different related or unrelated species. Thus, an ordinary practitioner would have been motivated to combine these methods to provide a rapid test for harmful algal bloom species that results in an added level of specificity compared with amplification assays based on traditional non-fluorescence methodologies. Because NASBA is an isothermal process that doesn't require heavy equipment such as thermocyclers, when combined with molecular beacon probes, this method is suitable for high through-put sample analysis and the development of automated workstations, and is also easily adapted for field-based testing. Because the method is ideally suited for amplifying RNA analytes using one reaction mixture, the application range is expanded beyond genomic targets to gene expression targets such as the mRNA product of the rbcL gene of *K. brevis.* Furthermore, the methods of Wilson provide a highly powerful approach to

species-specific detection since unique primer sets that can be designed for multiplexed assays (Wilson, p. 74, column 2, lines 3-8, and also those containing internal controls by using universal primers sets in conserved regions of the target gene (Wilson, p. 72, column 2, line 43 to p. 73, column 1, line 8).

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Yoon, which are 100% derived from sequences expressly suggested by the prior art of Yoon as useful for primers for the detection *K. brevis,* and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the

components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

(10) Response to Argument

Introduction

This application involves a central 35 U.S.C. 103(a) rejection of many of the claims and depends upon whether all of the claim elements are taught by the combination of Yoon, Buck and GenBank Accession No. AY119786. The remaining claims are rejected under Yoon in view of Bowers, Wilson, Buck and GenBank Accession No. AY119786 or under Yoon in view of Leone, Wilson, Buck and GenBank Accession No. AY119786.

Issue 1-Does the combination of Yoon, Buck and GenBank Accession No. AY119786 render the claims prima facie obvious?

Legal Standard

The legal standard for obviousness is based upon the factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Prima Facie Case

The prima facie case of obviousness is set forth in the rejection given above. The primary issue is whether the combined references teach each of the limitations of the claims. Appellant argues that the Examiner has mischaracterized the teachings of

Yoon. In particular, Appellant argues that Yoon does not teach a method for screening a sample for the presence of *K. brevis,* but instead teaches a method of determining the origin of plastids in red algae and dinoflagellates that involve amplification of *K. brevis* sequences from a pure sample rather than an impure sample. It has been established that Yoon teaches a method for amplification of a region of the *rbc*L gene of *K. brevis* (p. 11725, column 1, lines 13-24 and Table 2, supporting information). It is immaterial whether the sample used in the reference was pure or impure since the reference teaches a method for amplification of a target sequence that one of ordinary skill in the art would use to amplify the same or related sequences from a sample, regardless of purity.

Appellant then argues that Yoon does not teach a method using species-specific primers for amplification of a region of the *rbc*L gene of *K. brevis,* but rather only uses such primers for the *psa*A gene. Appellant is correct in stating that Yoon teaches the use of general primers for amplification of *K. brevis* sequences (see Table 2). However, further analysis of the 158-basepair sequence amplified by the *rbc*L gene primers taught by Yoon by a BLAST search revealed that the amplified sequence is unique to strains of *K. brevis.* Therefore, Yoon teaches species-specific detection of *K. brevis,* as is required to meet the limitation of claim 16 that a unique target region is amplified.

Appellant then argues that using the methods and primers taught by Yoon are not capable of species-specific detection of *K. brevis* in a sample because numerous species would provide false positives, such as the closely related *K. mikimotoi,* species of the sister genus *Karlodinium,* and possibly others such as those of the genus

Pavlova. As discussed above, based upon a BLAST search of the 158-bp sequence amplified by the primers taught by Yoon, at least a region of this sequence is unique to *K. Brevis*, even if the primers are only generally specific for the *rbc*L gene. Therefore, should the primers taught by Yoon detect this sequence in a related species such as *K. mikimotoi*, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to design other species-specific primers within the 158-bp sequence for the purposes of screening samples for specific detection of K. brevis. To this end, Wilson teaches methods of primer design for species-specific detection of microorganisms in water samples (p. 60, column 2, lines 5-16, p. 62, column 1, lines 35-40 and Figure 1). This method utilizes software that aligns sequences of related species to design primers that are specific to only one species in a sample containing large numbers of microorganisms and therefore is directly applicable to the design of primers to amplify organisms such as *K. brevis* in the presence of related organisms such as *K. mikimotoi* or other algae species.

Appellant then argues that the BLAST search used by the Examiner represents an exercise in hindsight in that the search does not establish that a primer sequence disclosed in a reference was known to be unique at the time of the reference or at the time the invention was made. The BLAST search reveals that the 158-bp sequence shared extensive homology with only strains of *K. brevis* and would have indicated homology with other species such as *K. mikimotoi* if they existed at the time the invention was made. It would also have been obvious to one of ordinary skill in the art at the time the invention was made to use a search tool such as BLAST to identify

unique regions in a target sequence such as the *rbc*L gene taught by Yoon and GenBank Accession No. AY119786, and to align sequences of related species for this region to design species-specific primers, using the methods of Wilson. Though the sequence listing in the NCBI database does not reveal whether the sequences are unique, Yoon has designed primers to amplify a segment (158 bp) of this sequence that detects *K. brevis.* Therefore, using the tools described above, one of ordinary skill in the art would be able to design species-specific primers for detection of *K. brevis.*

Issue 2-Does the combination of Yoon, Bowers, Wilson, Buck and GenBank Accession No. AY119786 render the claims prima facie obvious?

Prima Facie Case

The prima facie case of obviousness is set forth in the rejection given above. The primary issue is whether the combined references teach each of the limitations of the claims, including the use of real-time RT-PCR using specific primer pairs and a probe. As discussed above, the combination of Yoon, Buck and GenBank Accession No. AY119786 teaches a method for species-specific detection of K. brevis. Bowers teaches a method for detecting algal species such as the dinoflagellate *Pfiesteria piscicida* using real-time PCR and hybridization probes (p. 4643, column 1, lines 18-30 and p. 4645, column 1, lines 8-14), while Wilson teaches methods for designing species-specific primer sets by sequence alignment techniques (p. 60, column 2, lines 5-16, p. 62, column 1, lines 35-40 and Figure 1). The combination of these teachings would provide one of ordinary skill in the art at the time the invention was made with the

necessary elements to specifically detect *K. brevis* in a sample using real-time detection techniques.

Motivation to combine

The Federal Circuit has recently provided a detailed explanation of the subsidiary requirement for motivation to combine in Dystar v. Patrick Co., 80 USPQ 2d 1641, 1651(Fed. Cir. 2006) noting,

> "Indeed, we have repeatedly held that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the "improvement" is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal-and even common-sensical-we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him capable of combining the prior art references."

The Dystar court clarifies that motivation exists when the improvement results in a more desirable process and the issue then devolves to whether the ordinary artisan possesses the knowledge capable of combining the references. Here, where the ordinary practitioner is a Ph.D. with several years experience, there is no doubt that the ordinary artisan possesses the knowledge and motivation sufficient to prepare DNA fragments by homopolymer tailing for purposes of attaching adapters. Some of the listed motivations of Dystar, to result in a cleaner, more efficient, faster, cheaper and

more durable assay, would motivate the ordinary practitioner to perform fragment labeling and adapter attachment in a more efficient manner.

Appellant argues that an ordinary practitioner would not have been motivated to combine the Yoon, Bowers and Wilson references to provide a rapid test for harmful algal bloom species that results in an added level of specificity compared to those tests based on traditional PCR methods. As noted above, Yoon teaches the detection of a sequence specific to *K. brevis* in the *rbc*L gene using a reverse-transcriptase polymerase chain reaction method while Wilson teaches methods to design species-specific primers in order to detect single species in samples containing many different related or unrelated species. Since Bowers describes a real-time polymerase chain reaction combining species-specific primers with a cleavable species-specific fluorescent probe to detect harmful dinoflagellates such as *Pfiesteria piscicida*, an ordinary practitioner would have been motivated to combine these methods to provide a rapid, homogeneous assay for harmful algal bloom species that results in an added level of specificity compared with assays based on real-time PCR assays using SyBr Green or other intercalating dyes (Bowers, p. 4643, column 1, lines 18-39 and p. 4647, column 1, lines 4-10). Furthermore, in addition to a high level of specificity, the assay demonstrates high sensitivity, with a detection limit of 0.6 cell (Bowers, p. 4647, column 1, lines 25-29). Moreover, the use of a high through-put real-time PCR assay greatly improves upon other traditional methods of processing large numbers of environmental water samples such as scanning electron microscopy which are very labor-intensive, and also provides a method that is more easily adapted for field-based testing (Bowers,

p. 4643, column 1, lines 9-12 and p. 4647, column 1, lines 39-51). Finally, the methods of Wilson provide a highly powerful approach to species-specific detection using competitive PCR since unique primer sets that can be designed for multiplexed assays (Wilson, p. 74, column 2, lines 3-8, and also those containing internal controls by using universal primers sets in conserved regions of the target gene (Wilson, p. 72, column 2, line 43 to p. 73, column 1, line 8).

Appellant then argues that the Examiner relies on the court decision *In re Deuel* (51 F.3d 1552 (Fed. Cir. 1995) to reject the specific primers and probes claimed for real-time detection of *K. brevis*. Though *In re Deuel* remains relevant in such cases in that homologs of a known compound such as a nucleotide sequence can often have similar properties which may exhibit improved properties, there are more recent court decisions highly relevant to the current case with regard to obviousness. In the court decision *KSR International Co. v. Teleflex Inc., 82* 127 SCt 1727 (2007), the U.S. Supreme Court determined that if the combination of the claimed elements was "obvious to try" by a person of ordinary skill, this might show that such a combination was obvious under §103. Regarding "obvious to try", the Court stated:

"A person of ordinary skill is also a person of ordinary creativity, not an automaton. The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." Id., at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103."

In a recent Board decision, the "obvious to try" test was deemed particularly relevant with regard to nucleotide sequences, as summarized by the Board in Ex parte Kubin, 83 USPQ2d 1410 (Bd. Pat. App. & Int. 2007):

"General rule that it is improper to use prior art disclosure of particular protein, together with methods of isolating cDNA disclosed in other references, to reject claims drawn to specific nucleotide sequences on ground of obviousness is not viable to extent it rejects "obvious to try" test, since "obvious to try" may be appropriate test in more situations than previously contemplated; in present case, rule does not preclude finding that claimed nucleotide sequences encoding natural killer cell activation inducing ligand ("NAIL") polypeptide would have been obvious to person of ordinary skill in art based on prior art patent's disclosure of "p38" protein, which is same protein as NAIL, and patent's express teachings on how to isolate p38 cDNA by conventional techniques, since "problem" facing persons in art was isolation of NAIL cDNA, and there were limited number of methodologies for doing so, since skilled artisan would have had reason to try these methodologies with reasonable expectation that at least one would be successful, and since isolating NAIL cDNA thus was product ordinary skill and common sense, not innovation."

The Board emphasizes that the "obvious to try" test may be an appropriate test in more situations than previously contemplated, and is now considered more relevant with regard to claimed polynucleotides than *In re Deuel.*

Based on our findings and those of the Examiner, at least one of Appellants' claimed polynucleotides would have been obvious to one of ordinary skill in the art at the time Appellants' invention was made. Regardless of some factual similarities between Deuel and this case, Deuel is not controlling and thus does not stand in the way of our conclusion, given the increased level of skill in the art and the factual differences. See In re Wallach, 378 F.3d 1330, 1334, 71 USPQ2d 1939, 1942 (Fed. Cir. 2004) ("state of the art has developed [since] In re Deuel").

Appellants heavily rely on Deuel. (See, e.g., Br. 19.) To the extent Deuel is considered relevant to this case, we note the Supreme Court recently cast doubt on the viability of Deuel to the extent the Federal Circuit rejected an "obvious to try" test. See KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, ___, 82 USPQ2d 1385, 1394, 1396 (2007) (citing Deuel, 51 F.3d at 1559). Under KSR, it's now apparent "obvious to try" may be an appropriate test in more situations than we previously contemplated. When there is motivation to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103. KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, ___, 82 USPQ2d 1385, 1397 (2007). This reasoning is applicable here. The "problem" facing those in the art was to isolate NAIL cDNA, and there were a limited number of methodologies available to do so. The skilled artisan would have had reason to try these methodologies with the reasonable expectation that at least one would be successful. Thus, isolating NAIL cDNA was "the product not of innovation but of ordinary skill and common sense," leading us to conclude NAIL cDNA is not patentable as it would have been obvious to isolate it.

Thus, since the claimed primers and probe simply represent structural homologs of the sequences taught by Yoon, which are 100% derived from sequences expressly suggested by the prior art of Yoon as useful for primers and probes for the detection of *K. brevis,* and concerning which a biochemist of ordinary skill would attempt to obtain alternate primers with improved properties such as species-specificity, the claimed

primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Appellant then argues that the Examiner places undue emphasis on the equivalence of primers as supported by Buck and that the broad interpretation given to this reference would render all primers obvious. With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)." While the Appellant is correct in stating that Buck used a highly pure template for testing a large number of different primers, the evidence set forth by Buck still provides an ordinary practitioner with a reasonable expectation of success for successful amplification of a known sequence in an impure sample, after initially identifying candidate primers. To assist in deciding which sequences to amplify and selecting primers, Wilson teaches methods for designing species-specific primer sets by sequence alignment techniques (p. 60, column 2, lines 5-16, p. 62, column 1, lines 35-40 and Figure 1). This method utilizes software that aligns sequences of related species to design primers that are specific to only one species in a sample containing large numbers of microorganisms and

therefore is directly applicable to design of primers to amplify organisms such as *K. brevis* in the presence of related organisms such as *K. mikimotoi* or other algae species.

Issue 3-Does the combination of Yoon, Leone, Wilson, Buck and GenBank Accession No. AY119786 render the claims prima facie obvious?

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Appellant reiterates the argument that the combination of Yoon, Buck and GenBank Accession No. AY119786 does not render the base claim prima facie obvious. With regard to prima facie obviousness, Appellant argues that the claimed primers used for nucleic acid based sequence amplification (NASBA) are represented in the same nucleotide sequence as the target sequence, which is comprised in the sequence of GenBank Accession No. AY119786. Appellant also argues that the primers are claimed and not the target sequence. The basis for this rejection is identical to that applied in Issue 2 for claims 19-21, 24 and 25 except that the primers and probes are designed for use in a different mode of real-time amplification, NASBA. The primers and probes are homologs of the prior art sequence disclosed in Yoon and GenBank Accession No. AY119786 and therefore it is obvious to use the methods of Wilson to design species-specific primers for detection of *K. brevis* in a sample using the methods of NASBA taught by Leone (p. 2151, column 1, lines 6-15 and line 42 to column 2, line 12).

In summary, the rejections using Yoon in view of Buck and further in view of GenBank Accession No. AY119786, as well as the rejections using Yoon in view of Bowers and further in view of Wilson, Buck and GenBank Accession No. AY119786 and Yoon in view of Leone and further in view of Wilson, Buck and GenBank Accession No.

AY119786 teach all the elements of the claims and provide a proper motivation as required by the Federal Circuit and these rejections should be sustained.

(11) Related Proceedings Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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